Taste masked thin films printed by jet dispensing

Nikolaos Scoutaris, Martin Snowden, Dennis Douroumis[a]

[a]*Faculty of Engineering and Science, University of Greenwich, Medway Campus, Chatham Maritime, Kent ME4 4TB, UK*

[a] Corresponding author, Department of Pharmaceutical, Chemical & Environmental Sciences, Faculty of Engineering and Science, University of Greenwich, Medway Campus, Chatham Maritime, Kent ME4 4TB, UK. Tel.: +44 (0) 208 331 8440; Fax: +44 (0) 208 331 9805.
E-mail address: D.Douroumis@gre.ac.uk (D. Douroumis).

ABSTRACT

Taste masking of bitter active substances is an emerging area in the pharmaceutical industry especially for paediatric/geriatric medications. In this study we introduce the use of jet – dispensing as a taste masking technology by printing mucosal thin films of three model bitter substances, Cetirizine HCl, Diphenylhydramine HCl and Ibuprofen. The process was used to dispense aqueous drugs/polymer solutions at very high speed where eventually the drugs were embedded in the polymer matrix. The *in vivo* evaluation of jet – dispensed mucosal films showed excellent taste masking for drug loadings from 20 - 40%. Jet dispensing was proved to make uniform, accurate and reproducible thin films with excellent content uniformity.

Keywords: jet dispensing, printing, taste masking, water insoluble drugs

Printing technologies have been primarily used by the electronic industry but recently have been adopted for the fabrication of pharmaceutical dosage forms and drug delivery systems (Kolakovic et al. 2013). Applications include printing of dosage forms on porous substrates (Sandler et al. 2011), controlled release of active substances (Genina et al. 2012), multilayer film coatings (Preis et al. 2015, Buanz et al. 2014), microparticles (Sharma et al. 2013) bioprinting (Chang et al. 2011) or even transdermal microneedles (Uddin et al. 2015). A major advantage of printing technologies is the potential to be used for future fabrication of on – demand individualized medicines and regenerative medicines.

Jet dispensing is a technology that can dispense continuously liquids with a wider range of viscosities by moving the nozzle at high speeds across the x-axis and the stage across y-axis to cover all coordinates and jetting precise volume of dots. According to this technology (Fig. 1a,b), the jetting device operates in a continuous mode by using a pneumatic piston with a ball tip end to push fluid through a narrow orifice at the jet nozzle tip. The application of electrical signal triggers a solenoid, which allows air pressure to apply force on a ball-needle through a piston – seal. As the ball-needle is lifted from its seat, fluid is allowed to flow down and around the ball-needle tip. At the end of the electrical impulse, the solenoid discharges, releasing the air pressure allowing the force form the compressed spring to slam the ball-needle tip back down into its seat, separating and ejecting a dot from the fluid. By using the ball and seat design the coating solution fills the void left by the ball as it retracts from the seat. As the ball returns, the force due to acceleration breaks the stream of the drug – polymer solution, which is jetted through the nozzle. The broken stream of the solution strikes the substrate from a distance of 1.0mm to 3.5 mm above the board and forms an adhesive dot.

As shown in Fig. 1c we employed a laboratory DispenseMate 583 dispenser (Nordson - Asymtek, Maastricht, Netherlands) for the printing of taste masked mucosal films by using Cetirizine HCl (CTZ), Diphenylhydramine HCl (DPD) and Ibuprofen (IBU) as model drugs (Sigma, Gillingham, UK). A typical experiment comprised of ethanolic solutions of Eudragit EPO (Evonik Industries, Darmastadt, Germany) and CTZ or DPD or IBU at polymer/drug ratios of 90:10, 80:20 and 60:40 (wt/wt) printed on the dispenser's stage. CTZ and DPD are extremely bitter drugs and taste masking is quite difficult to achieve. In order to create the films, the solution was jetted in several parallel lines. For the purposes of the study the nozzle was moving in 9mm/sec jetting 1drop/0.03sec. The fluid pressure used was 11.4bar and the nozzle 100μm. The size of the ball tip and the seat was 2.4mm and 0.32μm respectively.

However, these settings can be altered according to solutions' properties and the film specifications. The parameter adjustments affect the dots in two different ways, either by changing properties of the fluid, or by changing mechanical properties of the jet. The nozzle orifice, the size of the seat, the size of the needle and the fluid pressure of the dispensed solution determines the droplets' size for given dispensing solution. The solution viscosities were kept at 30-50cP but highly viscous solution of 10,000cP can be easily printed by increasing the system pressure.

By applying jet dispensing we printed successfully EPO/CTZ, EPO/DPD and EPO/IBU thin films that can be used for drug mucosal delivery. As shown in Fig. 2 the films were printed with high accuracy, reproducibility and uniformity. The films appear glossy with a smooth surface even at high drug loadings ensuring high level of patient compliance. Ethanol evaporated instantly resulting in rapid film printing without further downstream processing. It is obvious that by adjusting the film dimensions the drug printed amounts can be easily tuned and adjusted to individual patient needs.

Fig. 3 depicts the differential scanning calorimetry (Mettler Toledo 823e, Greifensee, Switzerland) analysis, which revealed a glass transition at 58.17^{o}C for EPO and melting endotherms at 225.59^{o}C, 170.83^{o}C and 77.36^{o}C for CTZ, DPD and IBU respectively. In contrast, the DSC thermograms of all printed films showed the absence of drug melting peaks suggesting that all substances are in amorphous state in the polymer matrix. This resulted in high drug release rates (pH 7.4) from the films especially for the water insoluble IBU. The fact that EPO is highly permeable in pH >5 led to immediate release of the other two drugs (CTZ, DPD) as well. The highly water soluble CTZ and DPD were released within the first 5 min. From Fig. 4 it can be seen that EPO/IBU (60:40) demonstrated faster release rate compared to EPO/IBU (80:40). This has been previously observed and is attributed in strong intermolecular drug – polymer interactions through H-bonding (Gryczke et al. 2011). Nevertheless, IBU showed rapid release rates within 10min for both formulations. The film drug loadings were 20mg for CTZ/DPD and 50mg for IBU. Dissolution studies are carried out for all the formulations, employing USP dissolution apparatus at 37 ± 0.5^{o}C, rotated at constant speed of 50 rpm using 900 mL of simulative saliva (pH 7.4). The drug content uniformity was also evaluate for the printed films and it was found be excellent for all formulations with standard deviations varying from ±0.01 – 0.02mg (Madhavi et al. 2013).

In vivo taste masking evaluation of the printed films (Code of Ethics of the World Medical Association, Declaration of Helsinki) was performed on 10 healthy human volunteers. The films were held in the mouth for a period of 2min and then spat out. The bitterness was recorded immediately according to the bitterness intensity scale from 1 to 5, where 1, 2, 3, 4 and 5 indicate none, threshold, moderate, bitter and strong bitterness. Films did not disintegrate rapidly due to the EPO polymer, which requires pH<5 to dissolve. Fig. 5 shows that the perceived taste intensity studies in human volunteers showed complete taste masking for all drugs. The recorded bitterness scores were of 1 for the thin films, 3 for IBU and 5 for CTZ/DPD. Interestingly, the taste masking score was the same for the both IBU films with low and high drug loadings. The effective taste masking for all bitter drugs is attributed to the intermolecular interactions between the drug-polymer functional groups.

In conclusion, we demonstrated the efficiency of jet – dispensing to print rapidly oral thin films for mucosal delivery with excellent taste masking of bitter active substances. The technology can produce rapidly films with high palatability due to the printing reproducibility, uniformity and surface smoothness. Jet dispensing is versatile and it can print a wide range of drugs–polymer solutions by combining several polymers of various viscosities (e.g. mucoadhesive). Furthermore, it is feasible to tune the loading, release rates and dose of the drug substance and the film dimensions. The technology can be easily scaled – up for commercial purposes and manufacturing of robust taste masked thin films with future applications in personalized medicines.

References

Buanz, A.B., Belaunde, C.C., Soutari, N., Tuleu, C., Gul, M.O., Gaisford, S. (2014) Ink-jet printing versus solvent casting to prepare oral films: Effect on mechanical properties and physical stability. Int J Pharm., 2014, DOI: http://dx.doi.org/10.1016/j.ijpharm.2014.12.032

Chang, C.C., Boland, E.D., Williams, S.K., Hoying, J.B. (2011). Direct-write bioprinting three-dimensional biohybrid systems for future regenerative therapies. Journal of biomedical materials research. Part B, Applied biomaterials 98, 160-170.

Genina, N., Fors, D., Vakili, H., Ihalainen, P., Pohjala, L., Ehlers, H., Kassamakov, I., Haeggstrom, E., Vuorela, P., Peltonen, J., Sandler, N. (2012). Tailoring controlled-release oral dosage forms by combining inkjet and flexographic printing techniques. European

journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences 47, 615-623.

Gryczke, A., Schminke, S., Maniruzzaman, M., Beck, J., Douroumis, D. (2011). Development and evaluation of orally disintegrating tablets (ODTs) containing Ibuprofen granules prepared by hot melt extrusion. Colloids and surfaces. B, Biointerfaces 86, 275-284.

Kolakovic, R., Viitala, T., Ihalainen, P., Genina, N., Peltonen, J., Sandler, N. (2013). Printing technologies in fabrication of drug delivery systems. Expert opinion on drug delivery 10, 1711-1723.

Madhavi, RB., Murthy, VSN., Rani, PA., Gattu, DK. Buccal Film Drug Delivery System-An Innovative and Emerging Technology. Mol Pharm Org Process Res 2013, 1:3

Preis, M., Breitkreutz, J., Sandler, N. (2015). Perspective: Concepts of printing technologies for oral film formulations. Int J Pharm. DOI: 10.1016/j.ijpharm.2015.02.032

Sandler, N., Maattanen, A., Ihalainen, P., Kronberg, L., Meierjohann, A., Viitala, T., Peltonen, J. (2011). Inkjet printing of drug substances and use of porous substrates-towards individualized dosing. J Pharm Sci 100, 3386-3395.

Sharma, G., Mueannoom, W., Buanz, A.B., Taylor, K.M., Gaisford, S. (2013). In vitro characterisation of terbutaline sulphate particles prepared by thermal ink-jet spray freeze drying. Int J Pharm 447, 165-170.

Uddin, M.J., Scoutaris, N., Klepetsanis, P., Chowdhry, B., Prausnitz, M.R., Douroumis, D. (2015). Inkjet printing of transdermal microneedles for the delivery of anticancer agents. Int J Pharm. DOI: http://dx.doi.org/10.1016/j.ijpharm.2015.01.038

List of Figures

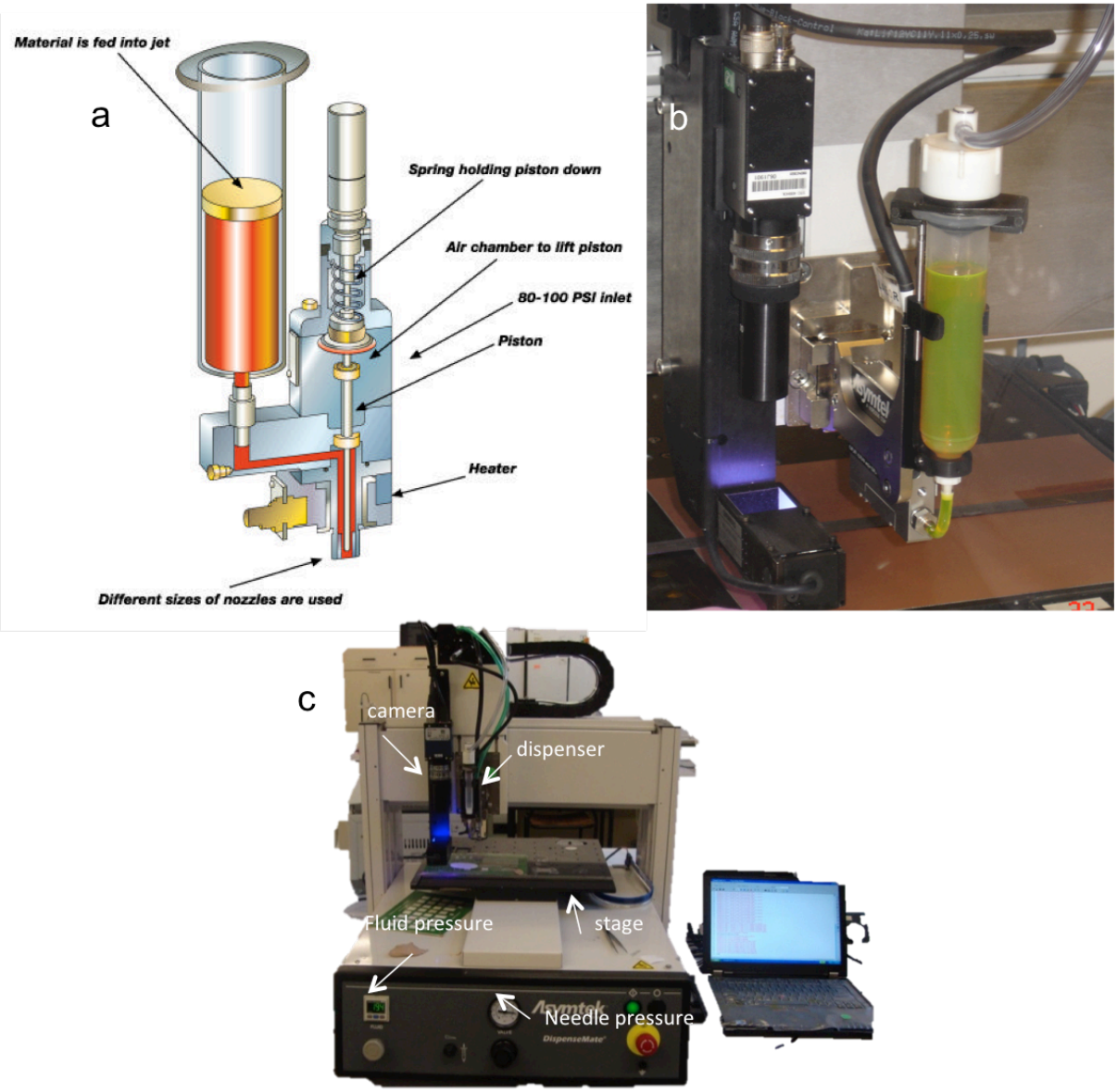
Fig. 1 a) Schematic diagram of a jet nozzle b) dispenser filled with printing solution, c) laboratory jet - dispenser

Fig. 2 Thin EPO/CTZ (80:20 wt/wt) films produced by jet dispensing of ethanolic solutions

Fig. 3 Typical DSC thermograms of bulk substances (EPO, CTZ, DPD), and printed thin films (EPO/IBU, 60:40 wt/wt)

Fig. 4 Drug release profiles of EPO/CTZ, EPO/DPD and EPO/IBU (n=3) at pH 7.4

Fig. 5 Taste masking evaluation of bulk substances and jet – dispensed thin films on healthy human volunteers (n=10)



175

176

177

178

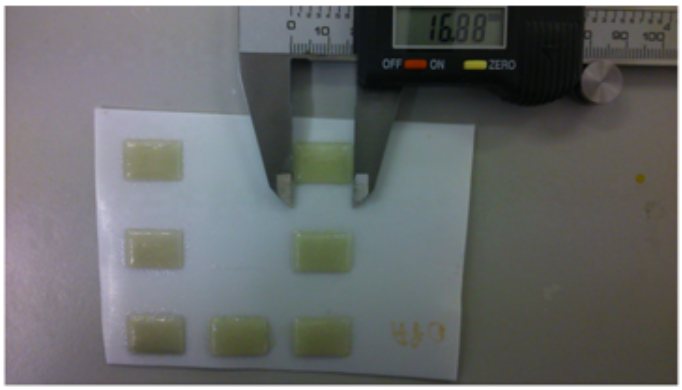
179

180

181

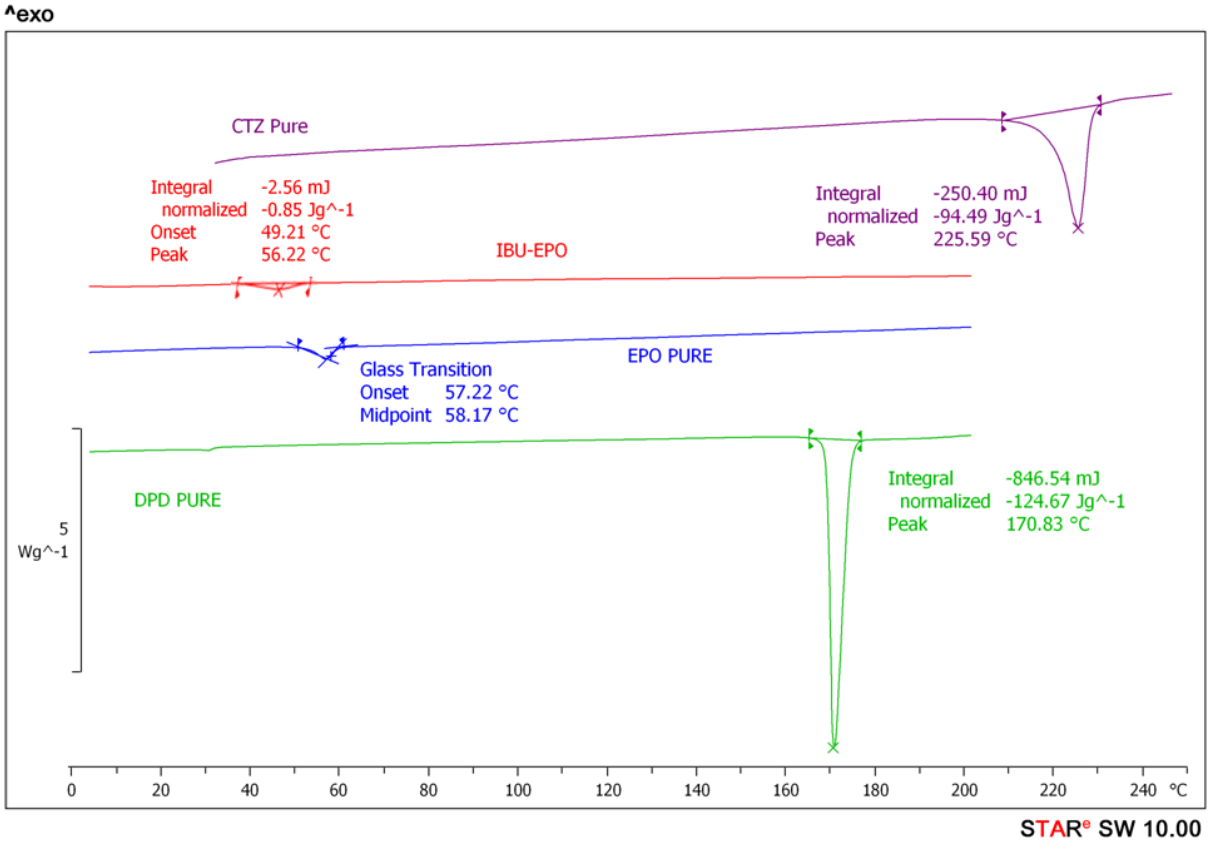
182

183



184

185



186

187

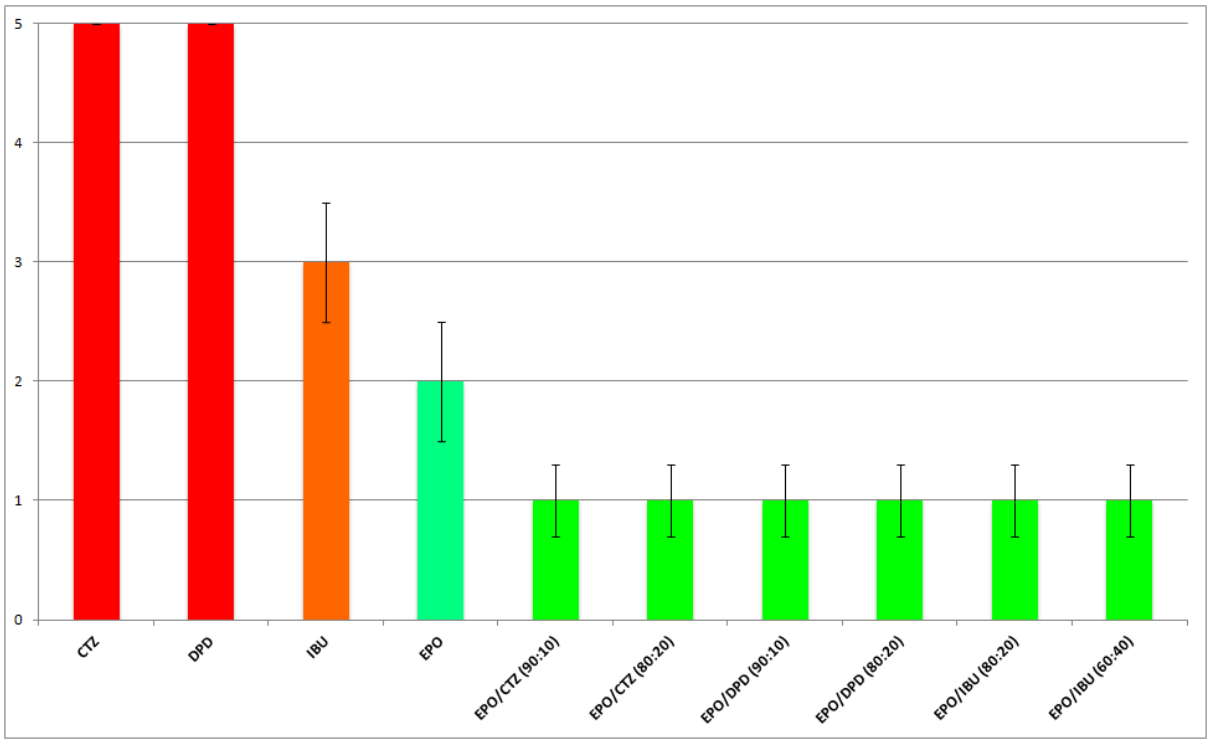
188

189

190

191

192


5
4
3
2
1
0
CTZ
DPD
IBU
EPO
EPO/CTZ (90:10)
EPO/CTZ (80:20)
EPO/DPD (90:10)
EPO/DPD (80:20)
EPO/IBU (80:20)
EPO/IBU (60:40)

193